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| 10/025,648      | 12/19/2001  | Henrik Bisgård-Frantzen | 4318.234-US         | 8501             |

25908 7590 07/29/2003

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PROUTY, REBECCA E

[REDACTED] ART UNIT

[REDACTED] PAPER NUMBER

1652

DATE MAILED: 07/29/2003

*[Signature]*

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                                      |  |
|------------------------------|--------------------------------------|--|
| <b>Office Action Summary</b> | Application No.<br><b>10/025,648</b> | Applicant(s)<br><b>Bisgard-Frantzen et al.</b> |
|                              | Examiner<br><b>Rebecca Prouty</b>    | Art Unit<br><b>1652</b>                        |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1)  Responsive to communication(s) filed on \_\_\_\_\_.

2a)  This action is FINAL.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

#### Disposition of Claims

4)  Claim(s) 30-47 is/are pending in the application.

4a) Of the above, claim(s) 40-47 is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 30-39 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims 30-47 are subject to restriction and/or election requirement.

#### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.

2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1)  Notice of References Cited (PTO-892)

4)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)

5)  Notice of Informal Patent Application (PTO-152)

3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6

6)  Other:

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Claims 1-29 have been canceled. Claims 30-47 are at issue and are present for examination.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 30-39, drawn to mutant  $\alpha$ -amylases, classified in class 435, subclass 202.
- II. Claims 40-47 drawn to DNA, vectors, host cells and expression of mutant  $\alpha$ -amylases, classified in class 536, subclass 23.2.

The inventions are distinct, each from the other because of the following reasons:

The DNA of Group II and the proteins of Group I are patentably distinct compounds because they are chemically different, the DNA has other utility besides encoding the proteins such as a hybridization probe and the proteins can be made by another method such as chemical synthesis.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Jason Garbell on 7-17-03 a provisional election was made without traverse to prosecute the invention of Group I, claims 30-39. Affirmation of this

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election must be made by applicant in replying to this Office action. Claims 40-47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is confusing and improperly dependent as it recites limitations which are excluded from the genus of alpha amylases of the claim 35 from which it depends. It is suggested that the claim be amended to recite "An isolated alpha amylase comprising an alpha amylase of claim 35 having amino acid substitutions of cysteine at positions equivalent to 349 and 428 of SEQ ID NO:3."

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Claims 30-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of variant  $\alpha$ -amylases having at least two mutations (i.e., deletion of residues equivalent to 179 and 180 of SEQ ID NO:3). The specification teaches the structure of only a few representative species of such variant  $\alpha$ -amylases each with only a small number of altered amino acids compared to the parent  $\alpha$ -amylases. However, the currently claimed genus includes variant  $\alpha$ -amylases with any number of alterations of the parent enzyme as long as amylase activity is maintained. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having  $\alpha$ -amylase activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

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Claims 30-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant of a parent  $\alpha$ -amylase having at least 80% homology to SEQ ID NO:3 wherein said variant has at least 80% identity to SEQ ID NO:3, has  $\alpha$ -amylase activity and comprises a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3 does not reasonably provide enablement for any variant of a parent  $\alpha$ -amylase having at least 80% homology to SEQ ID NO:3 wherein said variant has  $\alpha$ -amylase activity and comprises a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 30-34 are so broad as to encompass any variant of a parent  $\alpha$ -amylase having at least 80% homology to SEQ ID NO:3 wherein said variant has  $\alpha$ -amylase activity and comprises a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3. Thus, the currently claimed genus includes variant  $\alpha$ -amylases with any number of alterations of the parent enzyme as long as amylase activity is maintained. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant  $\alpha$ -amylases broadly encompassed by the claims. Since the amino acid sequence

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of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to only a few representative species of such variant  $\alpha$ -amylases each with only a small number of altered amino acids compared to the parent  $\alpha$ -amylases.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

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The specification does not support the broad scope of the claims which encompass all modifications and fragments of any because the specification does not establish: (A) regions of the protein structure which may be multiply modified without effecting  $\alpha$ -amylase activity; (B) a rational and predictable scheme for major modifications to  $\alpha$ -amylases having 80% homology to SEQ ID NO:3 at large numbers of residues with an expectation of obtaining the desired biological function; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any variant of a parent  $\alpha$ -amylase having at least 80% homology to SEQ ID NO:3 wherein said variant has  $\alpha$ -amylase activity and comprises a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of  $\alpha$ -amylases having the desired biological characteristics is unpredictable and the

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experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

It is noted that amending Claim 30 to insert "has at least 80% sequence identity to SEQ ID NO:3, and" following "wherein said variant" would overcome the rejections under 35 U.S.C. 112, first paragraph above.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-33, 35 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. (JBC 260:6518, 1989) in view of Bisgard-Frantzen et al. (WO95/10603).

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Suzuki et al. teach a mutant *Bacillus amyloliquefaciens*  $\alpha$ -amylase (BAA) with increased thermostability in which amino acid residues 176 and 177 (equivalent to residues 179 and 180 of SEQ ID NO: 3) are deleted.

Bisgard-Frantzen et al teach that the *Bacillus amyloliquefaciens*, *Bacillus stearothermophilus* and *Bacillus licheniformis* alpha amylases are homologous enzymes such that modification of corresponding residues in the three enzymes are expected to have similar effects. Bisgard-Frantzen et al. further teach an alignment of the amino acid sequences of the three enzymes which shows that positions 176 and 177 of BAA correspond to residues 179 and 180 of BST.

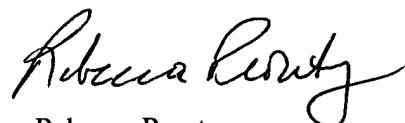
Therefore, it would have been obvious to one of ordinary skill in the art to introduce the mutations disclosed by Suzuki et al. into the corresponding positions of *Bacillus stearothermophilus*  $\alpha$ -amylase in order to produce a homologous  $\alpha$ -amylase which would have been reasonably expected to have similar improved properties in view of the known homology between these  $\alpha$ -amylases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rebecca Prouty  
Primary Examiner  
Art Unit 1652